

Approach to Regiochemistry Using Local Softness in 1,3-Dipolar Cycloadditions

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ABSTRACT: The principle of hard and soft acids and bases is applied in the local sense to rationalize the regiochemistry in the cycloaddition reactions of a few typical 1,3-dipoles, in particular those with phosphorus-containing dipolarophiles. Local softnesses are calculated using density functional theory. It is observed that the regioselectivity can be explained using these new reactivity descriptors based solely on the properties of the reactants. © 1998 John Wiley & Sons, Inc. *J Comput Chem* **19**: 195–202, 1998

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Introduction

The knowledge of the specific sites of interaction between two chemical species is of fundamental importance in determining the path and products of a given reaction. Chemists have always been interested in parameters that characterize the behavior of an atom in a molecule and thereby predict chemical reactivity. The concept of electronegativity can be taken as an example of such a parameter. Many empirical concepts, such as the hard and soft acids and bases (HSAB) principle,¹ have also been put forward to understand

and classify chemical reactions into various broad categories. It has recently been found that many useful and important classical chemical concepts (e.g., electronegativity, hardness, softness, etc.) appear naturally within density functional theory (DFT).² Thus, DFT not only gives a new status to these parameters but also provides a more rigorous method for their estimations. Keeping in mind the central role of electron density in DFT and its importance for understanding chemical reactivity, it is expected that DFT-based reactivity descriptors can provide a novel tool for interpreting a reaction mechanism. However, electron density by itself does not explain everything, and it is the response or change in electron density under the influence of an approaching reagent that is also of importance. Fortunately, DFT now provides us with many reactivity descriptors that specifically take this change in account. The Fukui function, $f(r)$, is

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an example at hand. The DFT-based reactivity descriptors such as the Fukui function, softness, and hardness have already provided a useful model for the interpretation of regioselectivity in many nucleophilic and electrophilic reactions.³⁻⁶

Very recently, Gazquez and Mendez⁷ have introduced a local version of the well-known HSAB principle. They propose that when two molecules, *A* and *B*, interact, then a bond would be likely to form between those two atoms of *A* and *B* whose Fukui function values are close to each other. They also propose that local softnesses play the same role as Fukui functions when global softness values of *A* and *B* are different. This proposal was subsequently verified in [4 + 2] cycloaddition reactions⁸ and in excited state photocycloaddition reactions.⁹ In both cases, it has been observed that the regioselectivity is completely determined by the local HSAB principle. In excited state photocycloaddition reactions between carbonyls and olefins we observed⁹ that the primary cycloadduct formed in obeying the local HSAB principle is always the predominant product. Local softness can also be used in explaining regioselectivity of free radical addition reactions¹⁰ and for the interpretation of asynchronism in [2 + 1] addition reactions.⁶

In the present study, we make an attempt to explain the regioselectivity in 1,3-dipolar cycloadditions. Cycloaddition reactions play an important role in synthetic organic chemistry, in particular with phosphorus compounds containing multiple bonds, due to the potential of forming many starting materials for the synthesis of P heterocycles. The problem of primary importance here concerns the regiochemistry of the cycloaddition. Although frontier molecular orbital theory (FMO) and perturbation molecular orbital theory (PMO) were found to be very successful in predicting the regiochemistry of products in these types of reactions, there are also cases that cannot be treated by such a simple procedure.¹¹ Nyulaszi et al.¹¹ studied the regioselectivity in a cycloaddition reaction between phosphacetylene and diazomethane and observed that the regioselectivity of the reaction is determined by the transition state itself.

When a dipolarophile, *A* = *B*, and a 1,3-dipole, *C* = *D* = *E*, approach each other, two cycloadditions are possible in principle (Fig. 1). However, it has been observed that, in a majority of cases, the reaction proceeds mainly through one transition state and thus introduces regioselectivity. Our aim in the present study is to use DFT-based reactivity concepts to rationalize this regioselectivity. More

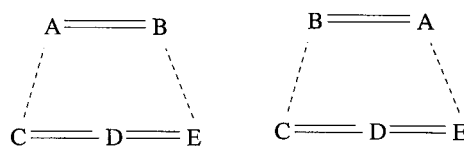


FIGURE 1. Approach of a dipolarophile and a 1,3-dipole.

specifically, we apply the HSAB principle in the local sense. The present study also examines the scope and limitations of these concepts, which is crucial to establish this new and alternative reactivity descriptor as an effective tool to interpret the reaction mechanism.

Theory and Computational Details

In density functional theory, the fundamental expression for the change in energy from one ground state to another is:

$$dE = \mu dN + \int \rho(r) \delta v(r) dr$$

where μ , $\rho(r)$, and $v(r)$ are the chemical potential, electron density, and external potential of the system, respectively. Hence, both μ and $\rho(r)$ can be regarded as a response function to the dN and $\delta v(r)$ perturbations, respectively. The first partial derivative of μ with respect to N , the total number of electrons, is the global hardness (η)¹²:

$$2\eta = \left[\frac{\partial \mu}{\partial N} \right]_{v(r)} = \left[\frac{\partial^2 E}{\partial N^2} \right]_{v(r)} = \frac{1}{S}$$

where S is the global softness. Due to the discontinuity of the energy vs. N curve, one generally makes a finite difference approximation to obtain S . In the finite approximation,¹² S can be written as:

$$S = \frac{1}{(IE - EA)}$$

where IE and EA are the first vertical ionization energy and electron affinity of the molecule, respectively.

The Fukui function $f(r)$ is defined as the first derivative of the electron density, $\rho(r)$, of a system with respect to the number of electrons, N , at

constant external potential, $v(r)^{13}$:

$$f(r) = \left[\frac{\partial \rho(r)}{\partial N} \right]_{v(r)} = \left[\frac{\delta \mu}{\delta v(r)} \right]_N$$

It, therefore, represents the response of the chemical potential of a system to a change in external potential. It has been argued¹³ that the greater the Fukui function value, the greater the reactivity of a site. Local softness, $s(r)$, is defined as:

$$s(r) = \left[\frac{\partial \rho(r)}{\partial \mu} \right]_{v(r)} = \left[\frac{\partial \rho(r)}{\partial N} \right]_v \left[\frac{\partial N}{\partial \mu} \right]_v = S \cdot f(r)$$

Because both $f(r)$ and $s(r)$ allow one portion of a molecule to be distinguished from another, they should be able to differentiate the reactive behavior of different atoms in that molecule. The condensed form of Fukui functions of an atom, say k , in a molecule with N electrons, has been proposed by Yang and Mortier¹⁴:

$$f_k^+ = [q_k(N+1) - q_k(N)] \quad \text{for nucleophilic attack}$$

$$f_k^- = [q_k(N) - q_k(N-1)] \quad \text{for electrophilic attack}$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)] \quad \text{for radical attack}$$

where q_k is the electronic population of atom k in a molecule. In view of the relation $s(r) = S \cdot f(r)$, the corresponding condensed local softness parameters can be expressed as¹⁵:

$$s_k^i = f_k^i \cdot S \quad i = +, -, 0$$

Local HSAB Principle

Let us now consider the interaction energy between two chemical species, A and B , one is electrophilic and the other nucleophilic. From a global point of view, and neglecting the change in external potential of A and B , the change in energy can be written as^{7,16}:

$$\Delta E_A = \mu_A \Delta N_A + (1/2) \eta_A (\Delta N_A)^2$$

and:

$$\Delta E_B = \mu_B \Delta N_B + (1/2) \eta_B (\Delta N_B)^2$$

Similarly, the change in grand potential can be expressed as¹⁶:

$$\Delta \Omega_A = -\frac{1}{2} \frac{(\mu_B - \mu_A)^2}{(S_A + S_B)^2} S_B^2 S_A$$

and:

$$\Delta \Omega_B = -\frac{1}{2} \frac{(\mu_B - \mu_A)^2}{(S_A + S_B)^2} S_A^2 S_B$$

To prove the HSAB principle, Chattaraj et al.¹⁶ have shown that, for a given chemical potential difference $\mu_A - \mu_B$ and a given S_B , the minimization of $\Delta \Omega_A$ with respect to S_A leads precisely to $S_A = S_B$. At the same time, the minimization of $\Delta \Omega_B$ with respect to S_B at fixed $\mu_B - \mu_A$ and S_A leads to $S_B = S_A$. Under these conditions, $(\Delta \Omega_A)_{\min} = (\Delta \Omega_B)_{\min}$. Basically, it implies that the grand potential of all the atoms in A and B becomes a minimum when A and B have an approximately equal global softness.

Gazquez and Mendez⁷ later extended this idea to the atomic level. When two molecules A and B form a new molecule AB , then the chemical potential of each atom of A and B would change from their initial value to become equal to μ_{AB} , the chemical potential of molecule AB . Thus, for each atom in A (say k) and B (say l), one can write⁷:

$$\Delta N_{Ak} = \frac{(\mu_B - \mu_A)}{(S_A + S_B)} S_B S_A f_{Ak}$$

and:

$$\Delta N_{Bl} = -\frac{(\mu_B - \mu_A)}{(S_A + S_B)} S_B S_A f_{Bl}$$

while the change in grand potential can be expressed as⁷:

$$\Delta \Omega_{Ak} = -\frac{1}{2} \frac{(\mu_B - \mu_A)^2}{(S_A + S_B)^2} S_B^2 S_A f_{Ak}$$

and:

$$\Delta \Omega_{Bl} = -\frac{1}{2} \frac{(\mu_B - \mu_A)^2}{(S_A + S_B)^2} S_A^2 S_B f_{Bl}$$

Now, if the interaction between A and B occurs through the k th atom of A and l th atom of B , then it is reasonable to assume that most favorable situation corresponds to:

$$(\Delta \Omega_{Ak})_{\min} = (\Delta \Omega_{Bl})_{\min}$$

which finally leads to:

$$S_{Ak} = S_{Bl}$$

Thus, the interaction between *A* and *B* is favored when it occurs through those atoms having softnesses that are approximately equal; that is, essentially the local HSAB principle.

In the present study, all DFT calculations were carried out with the B3LYP^{17,18} exchange correlation functional and using 6-31G(d,p) basis functions. For the large systems mentioned in Table IV, 3-21G basis sets were used for the calculations. The Fukui functions and atomic softnesses were evaluated from the formulas mentioned previously. The atomic charges were calculated by using the technique of electrostatic potential (ESP)-driven charges. It is well known that Mulliken charges are highly basis set dependent, whereas ESP-driven charges show less basis set dependence and are better descriptors of the molecular density distribution.^{19,20} Calculations were carried out with the Gaussian-94 program package,²¹ and atomic charges were calculated using the MK option.

Results and Discussion

Ab initio localized molecular orbital calculations,^{22–25} on a variety of dipolarophiles and 1,3-dipoles, established that electronic reorganization of the addition forming two new σ -bonds involves a cyclic movement of three π -type electron pairs and the most negative end of a reactant acts as a “ σ -bond donor” and, conversely, the other end as a “ σ -bond acceptor.” In a *normal* cycloaddition, the energetically favored one, the five-membered cycloadduct, is formed by a complementary disposition of the σ -bond donor and acceptor centers in both reactants (see Fig. 2).

It should be stressed that two possible mechanisms exist for these cycloadditions, namely the concerted and the biradical path. In this work, we consider only the concerted approach. Earlier study²⁶ using MCSCF calculations led to the conclusion that the energetically favored path turns out to be concerted one.

It was observed²⁷ that diazoalkanes undergo regiospecific [3 + 2] cycloaddition reactions of the

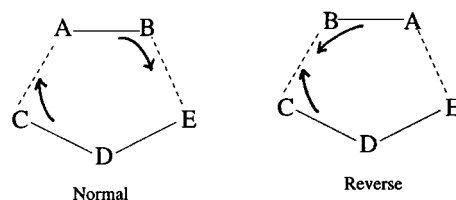


FIGURE 2. Two possible types of cycloaddition between 1,3-dipole and dipolarophile.

type shown in Scheme 1 with alkyl-substituted phosphaaalkynes. This is also the *normal* cycloaddition in the sense discussed previously.

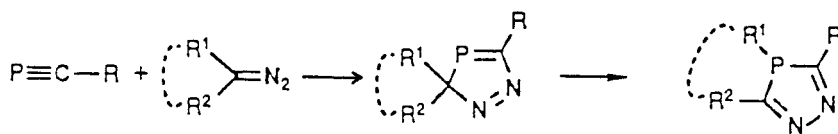
Nyulaszi et al.¹¹ observed from *ab initio* molecular orbital calculations that, in the case of cycloaddition between phosphaacetylene and diazomethane, the transition structure corresponding to the *normal* (structure 3 in Scheme 2) type of addition is lower in energy than the *reverse* one (structure 5 in Scheme 2) and the reaction proceeds, in reality, through the *normal* transition state.

In our present DFT model, we first classify the reactants as electrophilic or nucleophilic and then apply the local HSAB principle.⁷ However, to correlate the idea of the local HSAB concept and regioselectivity in this case, we need to define a quantity that suggests a measure of predominance of one reaction over the other. When atoms *i* and *j* of a molecule *A* are involved in the formation of a cycloadduct with atoms *k* and *l* of a molecule *B*, we can define a quantity:

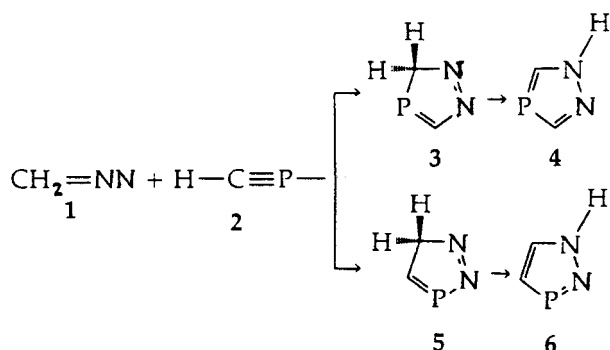
$$\Delta_{ij}^{kl} = (s_i - s_k)^2 + (s_j - s_l)^2$$

where s_i 's are the appropriate type of atomic softnesses (if s_i and s_j are electrophilic then s_k and s_l are obviously nucleophilic).

Δ_{ij}^{kl} is defined as the sum of squares of the softness difference values between atoms *i* and *j* of molecule *A* and atoms *k* and *l* of molecule *B*, respectively. One can similarly measure Δ for the reverse process ($i \rightarrow l$ and $j \rightarrow k$). The idea is based on the simultaneous fulfillment of the local HSAB concept at both termini. This is because, in



SCHEME 1.



SCHEME 2.

the case of the multicenter addition reaction, it is not the similarities of softness at one center that are important.

Δ can be considered a measure of how extensively the HSAB principle is satisfied. The reaction associated with a lower Δ value will be the preferred one. The results obtained for six phosphorus-containing dipolarophiles and three typical dipoles are recorded in Table I. In all cases, *normal* cycloadditions (see Fig. 2 and Table I for positions of atoms) are calculated to be energetically favorable to *reverse* cycloaddition (see, e.g., ref. 11). From the ionization energies and electron affinities of the dipolarophiles and dipoles it is observed that the direction of charge transfer is from the dipole to the dipolarophile, corresponding to a process with a smaller energy cost (Table I). Similar observations can also be made for other types of dipolarophiles.²² We thus take 1,3-dipole as a

nucleophile and dipolarophile as an electrophile for the 1,3-cycloaddition reactions. Hence, the appropriate Δ quantities for *normal* (Δ_n) and *reverse* (Δ_r) additions are defined as (see Fig. 2 for atom positions):

$$\Delta_n = (s_C^- - s_A^+)^2 + (s_E^- - s_B^+)^2$$

and:

$$\Delta_r = (s_C^- - s_B^+)^2 + (s_E^- - s_A^+)^2$$

Table II presents the global softness of the dipolarophiles and dipoles and atomic softnesses of the atoms involved in the cycloaddition reaction. The global softness of HN₃ is lower than all the dipolarophiles studied here, whereas the global softnesses of H₂CNN and H₂COO are comparable to those of the dipolarophiles. The carbon atom in H₂CNN and the N atom (bonded to H atom) in HN₃ have larger softnesses for nucleophilic attack than the other nitrogen atoms in the molecules. Table III gives the Δ values for both the *normal* and *reverse* types of additions between H₂CNN, HN₃, H₂COO, and phosphorus-containing dipolarophiles. One can easily notice that, for all cases considered, Δ_n is lower than Δ_r and thus the corresponding *normal* addition is favorable to the *reverse*. Thus, in the cycloaddition product, the C atom of H₂CNN or the N atom attached to the H atom in HN₃ or the terminal O atom in H₂COO is most likely to form a bond with the P atom in H₂CPH, HNPH, HPO, HPS, or HCP, or with the Si atom in H₂SiPH. This observation is in com-

TABLE I. Vertical Ionization Energies and Electron Affinities of P Dipolarophiles and Three Typical 1,3-Dipoles as Obtained from B3LYP Calculations Using the 6-31G(d,p) Basis Set.

	IE (eV)	EA (eV)	$\frac{H_2C = N \equiv N}{IE - EA^a}$	$\frac{HN = N \equiv N}{IE - EA^a}$	$\frac{O - O - CH_2}{IE - EA^a}$
Dipolarophile (B = A)					
H ₂ C = PH	10.11	-0.83	9.79 (11.73)	11.53 (12.26)	9.93 (11.00)
HN = PH	9.68	-0.21	9.17 (11.30)	10.91 (11.83)	9.31 (10.57)
O = PH	10.15	0.40	8.56 (11.77)	10.30 (12.30)	8.70 (11.04)
HP = SiH ₂	8.97	0.11	8.85 (10.59)	10.59 (11.12)	8.99 (9.86)
S = PH	9.24	1.34	7.62 (10.86)	9.36 (11.39)	7.76 (10.13)
HC \equiv P	10.63	-1.35	10.31 (12.25)	12.05 (12.78)	10.45 (11.52)
Dipole (C = D = E)					
H ₂ C = N \equiv N	8.96	-1.62			
HN = N \equiv N	10.70	-2.15			
O - O - CH ₂	9.10	-0.89			

^aIE_{Dipole} - EA_{Dipolarophile} (IE_{Dipolarophile} - EA_{Dipole}).

TABLE II. Global (*S*) and Local Softnesses for Nucleophilic (*s*⁺) and Electrophilic (*s*[−]) Attack Calculated from B3LYP Results.

Molecule	<i>S</i> (a.u.)	Atom (<i>k</i>)	<i>s</i> _{<i>k</i>} [−]	<i>s</i> _{<i>k</i>} ⁺
HN ₁ NN ₂	2.12	N ₁	1.03	0.57
		N ₂	0.94	1.15
H ₂ CNN ₁	2.57	C	2.03	0.13
		N ₁	1.18	1.27
H ₂ COO ₁	2.72	C	0.51	2.16
		O ₁	1.36	1.01
H ₂ CPH	2.49	C	1.36	0.41
		P	1.29	1.72
HNPH	2.75	P	1.66	2.11
		N	0.76	0.48
HPO	2.79	P	1.84	2.22
		O	0.52	0.35
H ₂ SiPH	3.07	Si	1.71	1.55
		P	1.40	1.36
HPS	3.44	P	1.43	1.83
		S	1.72	1.44
HCP	2.27	C	0.78	−0.01
		P	1.42	1.88

plete harmony with the other theoretical rationales or experimental observations.²⁶ Thus, the present model is clearly able to explain why *normal* addition is preferred over the *reverse* additions in these types of reactions. The present results are more striking if one notices that, as in the frontier orbital theory, the whole predictions are made purely from isolated molecular properties. Thus, some odd cases may appear, particularly when the perturbation due to the presence of other molecules is extremely high or some other type of stronger factor exists, such as a stereoelectronic effect. A closer look at Tables II and III reveals that, in the

normal type of addition, the softest center for electrophilic attack in the 1,3-dipoles forms a bond with the softest center for nucleophilic attack in the dipolarophiles. This result might suggest an asynchronous mechanism in which the interaction between the two softest atoms is proceeding faster than the other two centers. We are not aware of whether any experimental evidence exists supporting this view. However, the hypothesis formulated by Anh and coworkers,²⁸ indicating that “it is likely that the first bond would link the softest centers, i.e. the atoms giving the greatest overlap stabilization” is in line with our assumption.

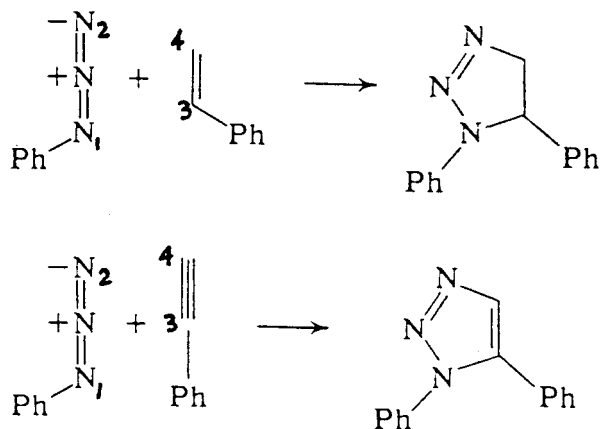
It is rather simple to generalize the application of the present approach to a larger set of partners. Here, we have selected a more realistic set of reactants to clarify its generality. Let us consider the cycloaddition reactions of phenyl azide with styrene and phenylacetylene. In both cases, it was observed²⁹ that the N atom attached to the phenyl ring in phenyl azide (N₁ in Scheme 3) preferentially forms a bond with the carbon atom attached to the phenyl ring (C₃ in Scheme 3) in styrene or phenylacetylene, which introduces a regioselectivity in the cycloaddition process (Scheme 3).

We analyzed these cycloaddition processes by the same procedure discussed earlier. Phenyl azide behaves as a nucleophile in these cycloadditions which can be confirmed from the ionization energies and electron affinities of these molecules. Table IV shows the softness values of the atoms involved in the cycloaddition reaction and also the corresponding Δ values. The global softnesses of phenyl azide, styrene, and phenylacetylene are nearly same. One can easily notice, once again from Table IV, that the predominant cycloaddition product is invariably associated with a lower Δ value, which

TABLE III. Δ Values (See Text for Definitions) for *Normal* (Δ_{*n*}) and *Reverse* (Δ_{*r*}) Types of Cycloaddition of Three Dipoles to P Dipolarophiles.

Dipolarophile	H ₂ C = N ≡ N (C = D = E) ^a	HN = N ≡ N (C = D = E)	O — O — CH ₂ (C = D = E)
(B = A)	Δ _{<i>n</i>} (Δ _{<i>r</i>})	Δ _{<i>n</i>} (Δ _{<i>r</i>})	Δ _{<i>n</i>} (Δ _{<i>r</i>})
H ₂ C = PH	0.69 (2.92)	0.76 (1.00)	0.14 (2.37)
HN = PH	0.49 (3.25)	1.37 (1.66)	0.56 (3.31)
O = PH	0.72 (3.89)	1.77 (2.10)	0.77 (3.94)
HP = SiH ₂	0.27 (0.58)	0.44 (0.47)	0.75 (1.07)
S = PH	0.10 (0.78)	0.89 (0.96)	1.08 (1.75)
HC ≡ P	1.44 (4.65)	1.62 (1.96)	0.54 (3.75)

^aIn *normal* cycloaddition, atom A of the dipolarophile forms a bond with atom C of the dipole.



SCHEME 3.

indicates that the product formed by maintaining the local HSAB principle is the preferred product observed experimentally.

Conclusion

Using DFT-based reactivity descriptors and a local version of the HSAB principle, we are able to explain the reason for the preference of a *normal* type of cycloaddition over the *reverse* type in the case of cycloaddition between 1,3-dipoles and P dipolarophiles. The quantity which can be taken as a measure of satisfaction of the HSAB principle is consistently lower for the *normal* type of addition. Applying the same argument, it is also possible to explain the regioselectivity in the cycloaddition reactions between phenyl azide and styrene or phenylacetylene. Thus, DFT-based reactivity descriptors can profitably be used in the interpretation of a reaction mechanism, particularly to understand the regioselectivity in addition reactions,

and to draw some insights about the cyclization mechanism. We would note that calculation of atomic charges is a major issue in the present approach as local softnesses are calculated from the approximate formula based on atomic charges. However, our earlier experience is that ESP-driven charges are more consistent for the calculations of local softness, although, in most cases, observations are the same whether one uses the Mulliken charge or the ESP-driven atomic charge.^{6,9,10} In the present study, local softnesses were also evaluated from the atomic charges based on Mulliken population analysis and natural population analysis (NPA) and the observations were same as discussed earlier, except in the case of H₂CNN, where some odd cases may appear if one uses Mulliken atomic charges. For all other cases, the observations are same, regardless of the method used for evaluation of atomic charges.

This paper is dedicated to Professor Norman Allinger on the occasion of his 70th birthday.

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TABLE IV.

Global, Atomic Softnesses and Δ Values (See Text for Definition) for Cycloaddition of Styrene and Phenylacetylene with Phenyl Azide.

Molecule	S (a.u.)	Atom	s_k^-	s_k^+	Δ_{12}^{34} (Δ_{12}^{43}) ^a
Ph—N ₁ NN ₂	2.81	N ₁	0.41	0.99	
		N ₂	0.65	1.10	
Ph—C ₃ H=C ₄ H ₂	2.90	C ₃	0.88	0.75	0.11 (0.42)
		C ₄	0.07	0.10	
Ph—C ₃ ≡C ₄ H	2.78	C ₃	0.05	0.00	0.17 (0.46)
		C ₄	0.75	0.60	

^a Δ_{ij}^{kl} indicates the softness differences when atoms *i* and *j* form bonds with atoms *k* and *l*, respectively, in the cycloaddition. Δ_{12}^{34} is associated with the experimentally observed preferred product.²⁹

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